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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	14

DATE MAILED: 07/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,416	LIU, XIANGJUN	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *13* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. In response to a restriction/election requirement mailed on January 8, 2003, Applicant cancelled claims 1-21 and added new claims 22-32, which correspond to cancelled claims 20 and 21.

2. Claims 22-32 are pending and will be examined.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on February 7, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

4. The drawings are objected to because:

A) Figure 1 has incomplete legend on the left-hand side. In a preliminary amendment filed on January 8, 2001, Applicant amended a description of Figure 1 to incorporate SEQ ID NOs. However, it is not clear what sequences these SEQ ID NOs correspond to in the figure, therefore Figure 1 needs to be corrected to incorporate SEQ ID NOs.

B) Figure 2 has two parts, Figure 2 and Figure 2A. It should be Figure 2A and 2B. In addition, legend of step 2 has typographical errors, such as "Nnon-ligated" and "prims".

C) In Figure 3, legend of step 2 has typographical errors, such as "Nnon-ligated" and "prims".

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

5. The disclosure is objected to because of the following informalities:

A) On page 16, [0052], lines 4 and 6, and on page 21, [0072], line 1: capitalized "Hybridization" in the middle of sentences.

B) On page 20, [0068], the last two lines: sequences start with "1". It is not clear what is the significance of the number in front of the sequence.

C) On page 21, [0069], second line: typographical error "fragment specific hybridized to … were eluted…".

D) On page 22, [0073], sequences start with "1". It is not clear what is the significance of the number in front of the sequence.

Appropriate correction is required. No new matter should be introduced.

Incorporation by Reference

6. Applicant indicated on page 7, [0030], that all patents and references cited are incorporated by reference. On page 9, [0037], Applicant cites "current Protocols in Molecular Biology" by Ausubel et al. and makes a statement that the teachings of the reference are incorporated by reference. On page 24, [0077], Applicant states that the references cited are incorporated into the patent application in their entirety.

7. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re*

Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

8. If the publications cited constitute a non-essential material, Applicant should include a statement to this effect (see MPEP 608.01(p), part A of which is cited below).

MPEP 608.01(p).

A. Review of Applications Which Are To Issue as Patents.

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, hyperlinks and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 22-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 22-32 are indefinite in claim 22 because claim 22 does not recite a final process

step, which clearly relates back to the preamble. The preamble states that the method is for detecting an allele via hybridization, but the final process step is "assaying the complex for specificity of different alleles". Therefore, it is unclear as to whether the claim is intended to be limited to a method of allele detection or a method of allele specificity assay.

B) Claims 22-32 are indefinite in claim 22 because claim 22 is indefinite over the recitation of "... wherein the oligonucleotides that are coupled to different bead sets are oligonucleotides with and without a spacer..." (emphasis added). It is not clear whether the oligonucleotides with spacers are coupled to different bead sets than oligonucleotides without spacers, or whether each of the different bead sets has oligonucleotides with and without spacers coupled to it. In addition, it is not clear whether the differences between bead sets are determined by the presence or absence of the spacers in oligonucleotides coupled to the beads.

C) Claims 22-32 are indefinite in claim 22 because claim 22 is indefinite over the recitation of "...assaying the complex for specificity of different alleles...". It is not clear what is encompassed by this step, since it is not clear what it means to assay a complex for allele specificity, or what "allele specificity" means, since "specificity" is a relative term.

D) Claims 25-32 are indefinite over the recitation of a phrase "any one of claims" before a claim number; for example, in claims 25-27 we have "any one of claims claim 22", in claims 28 and 29 "any one of claims claim 27", and in claims 30-32 "any one of claims 22". It is not clear what claims claims 25-32 depend from.

E) Claim 26 is indefinite over the recitation of "... coupling oligonucleotides with and without a spacer to different bead sets...". It is not clear whether the oligonucleotides with spacers are coupled to different bead sets than oligonucleotides without spacers, or whether each of the different bead sets has oligonucleotides with and without spacers coupled to it.

F) Claim 27 is indefinite over the recitation of "… further comprising obtaining a target nucleic acid sample containing multiple alleles…". It is not clear what is the relationship of the target nucleic acid sample to the target oligonucleotide of claim 22, and where in the method of claim 22 the step of claim 27 takes place.

G) Claim 30 recites the limitations "the template" and "the nucleic acid templates" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 22, from which claim 30 depends, does not contain a limitation " a template" or "a nucleic acid template".

H) Claim 32 is indefinite over the recitation of "… the bead sets that are coupled to the oligonucleotides with and without a spacer are conjugated with different oligonucleotides…" (emphasis added). It is not clear what is encompassed by the limitation "different oligonucleotides". Does "different" refer to the fact that some oligonucleotides have spacers, and some not, or to the fact that one set of oligonucleotides has spacers different from a second set of oligonucleotides, or to the fact that different oligonucleotides are different from each other?

I) Claim 32 is indefinite over the recitation of "… bead sets … can be identified by a fluorescence color ratio…". It is not clear whether "can be identified" refers to a property of the beads or to a method step of identifying the beads.

J) Claim 32 is indefinite over the recitation of "… the bead sets … are conjugated with different oligonucleotides…". It is not clear whether the phrase "conjugated with" refers to a property of the beads or to a step of conjugation of the beads to oligonucleotides.

Remarks concerning art rejections

11. Definition of an allele is used as provided by Applicant (page 5, [0019]): "A variant form of a given gene. Such variants include single nucleotide polymorphisms, insertions, inversions, translocations and deletions."

12. Claims 25-27 and 30-32 are treated as if they depended from claim 22, and claims 28 and 29 as if they depended from claim 27.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 22-29, 31 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Van Ness et al. (U. S. Patent No. 6,361,940 B1).

Regarding claim 22, Van Ness et al. teach combinations of oligonucleotides with different spacers which may be used in any reaction involving hybridization, such as genetic screening and amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single nucleotide polymorphism (SNP) detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The

specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer (col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Regarding claim 23, Van Ness et al. teach separation of allele-specific nucleic acid fragments (col. 60, lines 64, 65; col. 61, lines 26-30).

Regarding claims 24-26 and 32, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. Oligonucleotides specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 83, lines 10-67).

Regarding claim 27, Van Ness et al. teach polymorphism detection is samples containing CYP2D6 gene with 8 polymorphic sites (col. 97, lines 36-52).

Regarding claim 28, Van Ness et al. teach amplifying the gene fragment containing all of the polymorphisms (col. 98, lines 55-67).

Regarding claim 29, Van Ness et al. teach denaturing the target nucleic acid (col. 98, lines 9-11).

Regarding claim 31, Van Ness et al. teach HLA alleles (col. 63, lines 25-44).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 22-29, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneoka et al. (Biotechniques, vol. 10, p. 30, 32, 34, 1991) and Van Ness et al. (U. S. Patent No. 6,361,940 B1).

A) Regarding claims 22 and 31, Kaneoka et al. teach detection of HLA alleles by hybridizing a target nucleic acid with oligos, i.e., allele-specific primers (PSP 25 and Amp 1) coupled to bead sets to form a complex, followed by assaying the complex products (page 30, continued on page 32; page 32, second and third paragraphs).

Regarding claim 23, Kaneoka et al. teach separation of the allele-specific nucleic acid fragments on a sequencing gel (page 32, Figure 1).

Regarding claim 27, Kaneoka et al. teach purification of DNA containing the HLA-DR alleles (HLA-DRB1*0401-0408) from peripheral white blood cells (page 32, first paragraph).

Regarding claim 28, Kaneoka et al. teach amplification of the DNA with primers PSP 25 or Amp 1 (page 32, second paragraph).

Regarding claim 29, Kaneoka et al. teach converting double-stranded DNA to single-stranded DNA by denaturation (page 32, second paragraph).

B) Kaneoka et al. do not teach oligonucleotides with and without spacers coupled to different bead sets.

C) Van Ness et al. teach compositions and methods for increasing specificity of hybridization reactions.

Regarding claim 22, Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer (col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Van Ness et al. teach that combinations of oligonucleotides with different spacers may be used in any reaction involving hybridization, such as genetic screening, amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single base polymorphism detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Regarding claims 24-26 and 32, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to beads and labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. An oligonucleotide specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 83, lines 10-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used beads coupled to oligonucleotides with and without spacers of Van Ness et al. in the method of HLA-DR typing of Kaneoka et al. The motivation to do so, provided by Van Ness et al., would have been that using oligonucleotides with spacers provided increased specificity of primer or probe annealing to target (col. 42, lines 12-34), therefore allowing for accurate determination of allelic sequences.

17. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneoka et al. and Van Ness et al. as applied to claim 22 above, and further in view of Nolan et al. (Nature Biotech., vol. 16, pp. 633-638, 1998).

A) Claim 30 is drawn to confirming a sequence of the template by hybridizing the template with a second bead set complementary to the template and measuring hybridization of the templates by flow cytometry.

B) Regarding claim 30, Kaneoka et al. teach sequencing of the amplified target nucleic acids using the Amp 1 primer (page 32, third paragraph). Neither Kaneoka et al. nor Van Ness et al. teach detection of hybridization complexes by flow cytometry.

C) Nolan et al. teach flow cytometry for detection of molecular interactions, including assay for oligonucleotide hybridization on microspheres, which has been used to detect single nucleotide polymorphisms (page 637, fifth paragraph; Fig. 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used flow cytometry of Nolan et al. to detect hybridization complexes of the combined method of Kaneoka et al. nor Van Ness et al. The motivation to do so, provided by Nolan et al., would have been that flow cytometry discriminated between free and bound ligands without a washing step, had excellent sensitivity, and was used for multiplexing of detection reactions (page 634, second and third paragraphs; page 637, fourth paragraph).

18. Claims 22-29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000) and Van Ness et al. (U. S. Patent No. 6,361,940 B1).

A) Regarding claim 22, Armstrong et al. teach detecting SNPs (=alleles) using oligonucleotide probes coupled to fluorescently encoded microspheres (= beads). The probes are hybridized to fluorescently labeled PCR reaction products and the results are analyzed in a flow cytometer (Abstract). For each SNP, 15-17 probes were used, with each of the four dNTPs substituted for the variant base located in the middle of the probe, and each probe sequence was coupled to a fluorescently tagged microsphere. PCR-amplified genomic DNA was labeled with fluorescein, hybridized to the probes and, after washing away of the unbound PCR products, detected by flow cytometry (Fig. 1; page 102, the last paragraph, continued on page 103; page 103, the first paragraph).

Regarding claim 23, Armstrong et al. teach separation of the allele-specific hybridization products by flow cytometry (page 103, the first paragraph).

Regarding claim 24, Armstrong et al. teach probes specific for each of the SNPs coupled to different beads (Fig. 1; page 102, the last paragraph, continued on page 103).

Regarding claim 25, Armstrong et al. teach coupling of oligonucleotides specific for different polymorphisms to different bead sets (Fig. 1; page 102, the last paragraph, continued on page 103; page 103, third paragraph).

Regarding claim 27, Armstrong et al. teach obtaining genomic DNA samples from patients. The sample contained multiple alleles of the following genes: ADRB, APOE, CHRM2, COMT, HTR1B1, HTR1B2, KLK2 and UGT (page 104, first and second paragraphs).

Regarding claim 28, Armstrong et al. teach amplification of the genomic target nucleic acid (page 104, first and fourth paragraphs).

Regarding claim 29, Armstrong et al. teach denaturing of the double-stranded target nucleic acid into single strands (page 102, the last paragraph, continued on page 103; page 104, second paragraph).

B) Armstrong et al. do not teach oligonucleotides with and without spacers.

C) Van Ness et al. teach compositions and methods for increasing specificity of hybridization reactions.

Regarding claim 22, Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer

(col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Van Ness et al. teach that combinations of oligonucleotides with different spacers may be used in any reaction involving hybridization, such as genetic screening, amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single base polymorphism detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Regarding claims 24-26 and 32, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to beads and labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. An oligonucleotide specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 83, lines 10-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used beads coupled to oligonucleotides with and without spacers of Van Ness et al. in the method of SNP typing of Armstrong et al. The motivation to do so, provided by Van Ness et al., would have been that using oligonucleotides with spacers provided increased specificity of

primer or probe annealing to target (col. 42, lines 12-34), therefore allowing for accurate determination of allelic sequences.

19. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000) and Van Ness et al. (U. S. Patent No. 6,361,940 B1) as applied to claim 22 above, and further in view of Long (Encyclopedia of Immunology, Roitt, I. M., Editor, Academic Press, San Diego, pp. 686-688, 1992).

A) Claim 31 is drawn to the target oligonucleotide being an HLA allele.

B) Neither Armstrong et al. nor Van Ness et al. teach target nucleotides with HLA alleles.

C) Long teaches HLA class II alleles (DP, DQ and DR), determination of which is necessary for matching donor and recipient in organ transplantation, and typing of HLA alleles by PCR (Fig. 1; page 687, fourth and fifth paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used HLA allele-containing target oligonucleotide of Long in the combined method of Armstrong et al. and Van Ness et al. The motivation to do so, provided by Long, would have been that HLA allele determination was used for correct matching of organ transplants.

20. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization

where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
July 10, 2003 TS

B. J. FORMAN
PATENT EXAMINER